Treatment of Peripheral Non–Small Cell Lung Carcinoma with Stereotactic Body Radiation Therapy

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On behalf of the IASLC Advanced Radiation Technology Committee

Abstract: Stereotactic body radiation therapy (SBRT) is an effective and well-tolerated noninvasive treatment for medically inoperable patients with peripheral non–small cell lung carcinoma. The term "peripheral" refers to lesions that lie 2 cm or more from the mediastinum and proximal bronchial tree and was instituted based on results from a specific dose and fractionation schedule. Improvements in immobilization, respiratory motion management, and image guidance have allowed for SBRT's highly conformal and accurate delivery of large radiation doses per fraction. Results from prospective and retrospective studies suggest that lung SBRT has superior outcomes when compared with conventionally fractionated treatments and is comparable with surgical resection. Investigations into the optimal SBRT dosing regimen for peripheral lesions are ongoing, with recent trials suggesting comparable efficacy between single and multiple fraction schedules. Chest wall toxicity after peripheral treatment is common, but it usually resolves with conservative management. Pneumonitis is less often observed after treatment of peripheral lesions, and changes in pulmonary function tests are minimal. Studies in the frail and elderly suggest that neither baseline pulmonary function tests nor age should preclude treatment. Recent technical developments have reduced delivery time and resulted in more conformal treatments. This review is on behalf of the IASLC Advanced Radiation Technology Committee.

Key Words: SBRT, NSCLC, Lung cancer.

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With the recent finding that computed tomography screening of patients at high risk for developing lung cancer can reduce both cancer-related mortality and overall mortality, cancer screening of patients with reasonable life expectancies and significant smoking histories is increasingly being encouraged. With such screening, non–small cell lung cancer (NSCLC), the most common lung cancer histology, will likely be identified more often and in earlier stages than in the past.[1] While surgery is still the preferred definitive treatment for patients with early stage lung cancer, many patients have significant cardiac and pulmonary comorbidities often related to tobacco abuse that put them at high risk for complications and disability from surgical resection. For patients with such comorbidities or for patients who refuse invasive treatments, stereotactic body radiation therapy (SBRT) has emerged over the past decade as the standard of care for the medically inoperable patient with early stage lung cancer.

SBRT differs from conventionally fractionated radiation therapy in many ways. Instead of delivering radiation in small doses over a course of several weeks, SBRT delivers radiation at very high doses and extremely precisely to carefully delineated targets over a brief period, typically no more than 1 to 2 weeks. There are some variations in definitions such that the American Society for Radiation Oncology limits SBRT to a maximum of five fractions, but the European Organization for Research and Treatment of Cancer allows SBRT in up to eight fractions. Improvements in tumor staging, target delineation, treatment planning, patient immobilization, respiratory motion management, and image guidance now allow for the reproducible delivery of these few, but large doses of radiation to a tumor with narrow margins. Delivery of these larger fractions allows for a higher biologically effective dose than with conventionally fractionated radiation therapy. At the same time, the narrower margins and sharper drop-off of dose (dose gradient) from the target help minimize injury to surrounding normal tissue.

The location of this dose gradient ultimately determines the toxicity, but not the efficacy of SBRT. A prospective phase II study at Indiana University was the first to demonstrate that treatment of central and perihilar tumors had a higher risk of severe toxicity than treatment of peripheral tumors.[2] This central region was defined as within 2 cm of the proximal bronchial tree (Fig. 1). All patients in this study received 60 to 66 Gy in three fractions. Those with central tumors had nearly a threefold increase in the rate of severe toxicity. With 4 years of follow-up, the rate of severe toxicity was 10% in patients with peripheral tumors versus 27% in patients with central tumors.[3] However, there was no difference in the 95% local control rate or median overall survival of 33 months by location. Several other studies have since showed similar differences in toxicity, but not significant differences in overall survival between central and peripheral tumors (Table 1).

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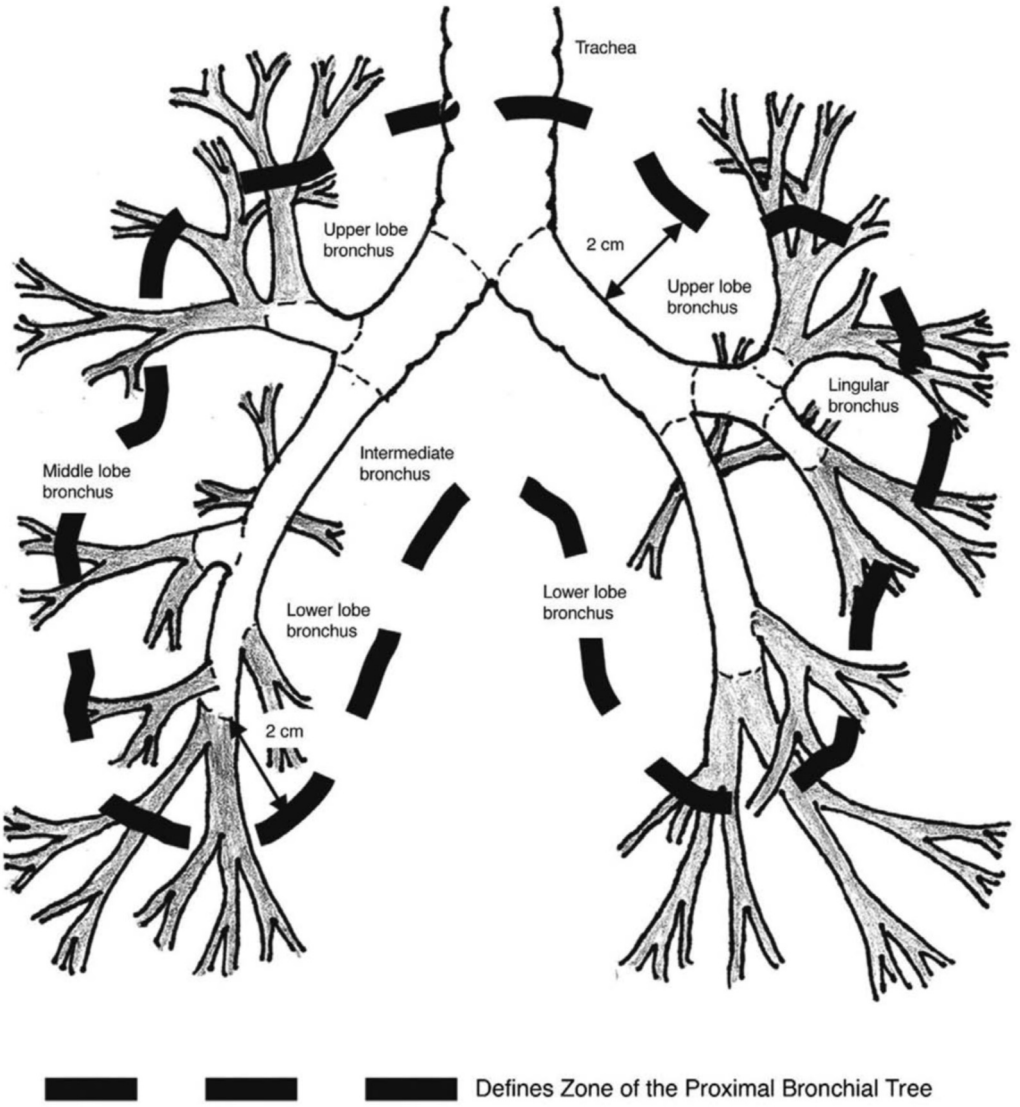

FIGURE 1. Diagram showing the definition of the central tumor region, also known as the zone of the proximal bronchial tree. Copyright American Society of Clinical Oncology.

TABLE 1. Studies Comparing Central Versus Peripheral NSCLC Lesions Treated with SBRT

	Patients			Overall Survival			Local Control			Severe Toxicity		
Institution	**P**	**C**	**F/u (Years)**	**P (%)**	**C (%)**	***p***	**P (%)**	**C (%)**	***p***	**P (%)**	**C (%)**	***p***
Asan Medical Center[4]	23	9	2	35	50	0.85	84	89	0.97	0	33	-
Erasmus MC-Daniel den Hoed[5]	32	6	2	50	17	0.07	100	100	-	-	-	-
Indiana University[3]	48	22	3	-	-	0.70	-	-	-	10	27	0.09
Julius- Maximilians University[6]	26	6	3	-	-	-	-	-	-	16	9	-
Nagoya City University[7]	145	35	3	71	79	0.18	85	78	0.45	-	-	-
Technische Universität München[8]	68	24	3	41	29	0.65	89	64	0.04	-	-	-
University Hospital Brussels[9]	23	17	2	-	-	-	91	94	0.07	16	40	0.06
Washington University in St. Louis[10]	111	11	2	60	90	0.21	91	100	0.46	0	0	-
Yale University[11]	183	70	2	56	52	0.56	90	83	0.33	7	3	0.15

P, peripheral; C, central; F/u, follow-up; -, not reported; SBRT, stereotactic body radiation therapy; NSCLC, non–small cell lung carcinoma.

However, these comparisons remain limited by the smaller number of central lesions that have been treated and reported. It should be emphasized that this concept of "peripheral" versus "central" lesions is closely linked to the dose and fractionation employed. For example, longstanding series from Japan have not historically reported such location-dependent toxicity rates when lower doses like 10–12 Gy per fraction have been utilized.

OUTCOMES

Fractionation

Due to the toxicity concerns raised by Indiana, the multi-institutional phase II RTOG 0236 limited enrollment to patients with peripherally located tumors. Without correcting doses to the low density of the lung, this trial used homogeneous prescription doses of 60 Gy in three fractions. A subsequent analysis of phantom dosimetry obtained during institutional credentialing for RTOG 0236 showed that the equivalent heterogeneous dose prescription was 54 Gy in three fractions.[12] The study showed a 3-year primary tumor recurrence rate of 2%, a 3-year locoregional failure rate of 13%, and a median survival of 4 years, more than double that expected with conventionally fractionated radiation therapy.[13] RTOG 0236 was recently updated showing a 5-year primary tumor recurrence rate of 7%, a 5-year locoregional recurrence rate of 38%, and a median overall survival of 4 years.[14] These results have been replicated in numerous studies of peripheral lesions (Table 2).

Since there is no data yet published supporting the overall efficacy of one fractionation schedule over another, there are a variety of lung SBRT schedules described in the literature applicable to peripheral tumors. Perhaps the most extreme schedule involves single-fraction-based therapy. Early reports show SBRT doses being escalated from 15 Gy to 34 Gy with increasing success.[22] At a single dose greater than or equal to 30 Gy in one study, the local control rate was 83% with an overall survival of 41% at 2 years. The only grade 3 toxicity in this high dose peripheral cohort was in a patient with active tuberculosis.[23] Several other groups had no greater than or equal to grade 3 toxicities in their high dose single fraction cohorts.[24,25] A recent retrospective single institution comparison of 30 Gy versus 34 Gy in a single fraction in 80 patients found no significant difference in toxicity, as well as no difference in 1-year overall and lung cancer-specific mortality.[20]

To more formally address the question of radiation dose and fractionation for peripheral tumors, RTOG 0915 is the first randomized phase II trial comparing 34 Gy in a single fraction versus 48 Gy in four fractions. With a median follow-up of just under 2 years, primary tumor control was 97% in both arms. Overall survival at 1 year was 85% in the single fraction arm and 91% in the four fraction arm. Protocol-specified adverse events occurred in 10% of the single fraction patients and 13% of the four fraction patients.[16] If these results are maintained with longer follow-up, a phase III trial comparing a single fraction of 34 Gy compared with 54 Gy in three fractions (per RTOG 0236) has been proposed with a primary endpoint of overall survival.

With the results of such a trial, one would hope to build a consensus around the optimal number of fractions in lung SBRT for peripheral tumors. There continues to be considerable variation in treatment choice in the United States. For peripheral T1N0 tumors, only 1% of practicing radiation oncologists would use a single fraction. Most (56%) would use a three fraction regimen, with less choosing a four (18%) or five (25%) fraction regimen.[26]

Surgical Comparisons

Comparisons of local control of SBRT to surgery remain challenging and controversial, and these comparisons are not limited to the subsets of peripheral versus central lung tumors. A meta-analysis comparing 40 SBRT studies and 23 surgery studies found that after adjusting for the proportion of operable patients and age, SBRT and surgery had similar estimated overall and disease-free survival.[27] Matched pair and propensity score comparisons of outcomes within individual academic institutions demonstrate similar overall survival, local-regional control, and distant control when controlled for

TABLE 2. Selected Series of Patients with Peripheral NSCLC Lesions Treated with SBRT

Location	Patients	Dose/Fxs	Cohort	Time (Years)	OS (%)	LC (%)	Grade 3+ Toxicity (%)
RTOG 0236, USA[14]	55	54/3	P	5	40	93	31
Sweden, Norway, & Denmark[15]	57	66/3	P	3	60	92	30
RTOG 0915, USA[16]	45	48/4	P	1	91	98	13
RTOG 0915, USA[16]	41	34/1	P	1	85	97	10
University of Miami, USA[17]	31	60–67.5/3–5	R	4.5	84	86	0
Hokkaido University, Japan[18]	41	40–48/4	R	3	47	57	5
University of Virginia, USA[19]	40	42–60/3–5	R	2	45	83	2
Cleveland Clinic, USA[20]	25	34/1	R	1	64	86	0
Cleveland Clinic, USA[20]	55	30/1	R	1	75	98	0
University of Heidelberg, Germany[21]	32	26–30/1	R	1	-	100	0

Dose is reported in total Gy over number of fractions.

OS, overall survival; LC, local control; P, prospective cohort; R, retrospective cohort; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; NSCLC, non–small-cell lung carcinoma.

patient selection factors.[28,29] A single institution comparison of lobectomy and SBRT showed comparable patterns of failure for clinical stage I NSCLC.[30] Only lobar control differed, but not primary tumor, regional, or distant control. This was despite 33% of surgery patients being upstaged by pathology and 20% of surgery patients receiving adjuvant chemotherapy, whereas none of the SBRT patients received adjuvant chemotherapy.

Unfortunately, all randomized studies attempting a prospective comparison between surgery and SBRT have failed. The randomized phase III studies Dutch ROSEL, RTOG 1021/ACOSOG Z4099, and the STARS trial at M.D. Anderson have all been terminated secondary to slow patient accrual. However, a combined analysis of those who were enrolled and randomized on ROSEL and STARS showed a significant 3-year overall survival advantage in favor of SBRT, 95% versus 79% ($p = 0.037$). With a median follow-up of 3 years and a total of 58 patients, recurrence-free survival was comparable at 86% and 80% ($p = 0.54$) between SBRT and surgery. The majority of those treated with SBRT (87%) had peripheral lesions. Only 10% of patients treated with SBRT developed grade 3 toxicity, whereas 44% treated with surgery developed grade 3 and 4 toxicities. The only treatment-related death occurred in the surgery group. Although the patient numbers are small, this combined analysis suggests "at least equipoise between the two modalities" and that lobectomy with nodal dissection or sampling "results in an increased rate of procedure-related mortality and morbidity" when compared with SBRT.[31]

Apart from additional randomized studies between surgery and SBRT, prospective cohorts of operable patients electing for SBRT will likely be the strongest evidence obtainable. RTOG 0618 is a completed phase II trial that looked at the use of SBRT in those patients with biopsy-proven peripheral NSCLC, who were deemed operable. It has shown a 2-year primary tumor failure rate of 7.7%, a 2-year involved lobe failure rate of 19.2%, and a 2-year overall survival rate of 84.4%.[32] JCOG 0403 is a similar Japanese phase II study which for operable patients has shown a 3-year local progression-free survival rate of 68.5% and 3-year overall survival rate of 76%.[33]

TOXICITY

Chest Wall

Treatment of peripheral lesions may result in the chest wall receiving significant collateral dose. Damage to the chest wall may be expressed as skin, soft tissue, bone, and neurologic symptoms. Skin changes include acute erythema and ulceration as well as late hyperpigmentation and fibrosis. Acute skin changes typically occur 3 to 6 weeks after treatment and severe toxicities are rare, seen in less than 10% of patients treated. The use of more than three beams and keeping the skin dose to less than half of the tumor prescription dose have been statistically linked to improved skin outcomes.[34] Limiting dose to the skin can be challenging, however, particularly in patients with tumors abutting the pleura and with a higher body mass index.[35]

Whereas almost all surgical patients will experience de facto chest wall pain due to the inherent invasiveness of the treatment, lung SBRT to peripheral lesions only produces neuropathic pain and symptomatic rib fractures in a minority of patients. Management replicates that used for surgical patients and is conservative. Anti-inflammatory medications are the primary analgesic followed by gabapentin or narcotics if required.[36] Pain requiring intervention has been reported in up to 24% of patients and rib fracture in up to 42% of those with peripheral tumors treated by SBRT.[37,38] However, around two-thirds of rib fractures will be asymptomatic.[39] To date, no grade five chest wall toxicity has been reported. Female gender and obesity have been linked in multiple studies to increased chest wall toxicity. Patient predictive factors are not clearly defined, however. Studies conflict on whether younger[40] or older[41] patients are more susceptible. With respect to radiation delivery, the maximum dose delivered to the chest wall and the volume of chest wall receiving 30 Gy have been predictive of toxicity in multiple studies.[42] Only recently has chest wall and rib delineation been required when planning treatments on multi-institutional trials, although a consensus dose constraint has yet to defined.

Pneumonitis

A historic concern with delivering higher effective doses to the lung with lung SBRT has been the potential for increasing pulmonary toxicity in patients with already limited respiratory reserve. Of note, grade three to four pulmonary complications occurred in 16% of the patients with peripheral tumors in RTOG 0236.[13] However as noted by the authors, these findings were not primarily patient symptom related but rather related to prespecified changes in pulmonary function tests (PFTs). In contrast to conventionally fractionated radiation where the mean lung dose and the volume of lung receiving 20 Gy predict for pneumonitis, toxicity with peripheral SBRT does not correlate with any such dosimetric parameters. Sharp dose gradients and the fact that peripheral tumors are far from large airways likely are responsible for this minimal toxicity when compared with studies of central lesions. It remains difficult, nonetheless, to separate treatment toxicity from exacerbations of underlying pulmonary disease common in lung cancer patients.

Several retrospective studies have concluded that PFTs change minimally[43] after SBRT for peripheral lesions and that poor baseline PFTs do not correlate with decreased survival.[44,45] More interestingly given that it was a prospective, multi-institutional study, in RTOG 0236, the mean percent decline in forced expiratory volume in 1 second and the mean percent decline in diffusing capacity for carbon monoxide were both 6% 2 years following treatment.[46] There were minimal changes in arterial blood gases after treatment, and there were no significant changes in oxygen saturation. Baseline PFT values did not predict for pneumonitis or decreased overall survival when adjusted for cardiac comorbidity. Thus, lung SBRT remains a safe modality in a very fragile population, and poor PFTs should not be used to exclude patients from treatment.

Elderly

Inasmuch as poor baseline pulmonary status should not exclude patients with peripheral NSCLC from lung SBRT,

neither should patient age. A study of patients over the age of 75 years showed a 3-year local control of 89%, a 3-year overall survival of 45%, and grade three toxicity limited to less than or equal to 10% of patients.[47] The majority (84%) in this study had peripheral tumors. A study of octogenarians in which all but one patient had peripheral disease reported no severe toxicity after SBRT and a 2-year overall survival of 74% with no local failure.[48] National population-based studies of the elderly with early stage NSCLC have shown that an increase in the utilization of SBRT over time leads to an increase in overall survival. This survival increase is limited to those treated with radiation and is not observed in those who received surgery or no treatment over the studied time periods.[49] Overall, tolerance of SBRT has proven comparable with younger patients.[50]

DELIVERY

SBRT is often delivered using 7–12 noncoplanar static beams with each day of treatment lasting between 20 and 45 minutes including patient set-up, verification, and treatment delivery. However, prolonged treatment sessions are associated with intrafractional shifts in the position of both tumor and patients. If treatments take longer than half an hour, mean intrafraction tumor deviation may exceed 5 mm.[51] Attempts to decrease treatment time and therefore these shifts include removing flattening filters[52] from the beam to increase the dose rate, as well as treatment with arcs,[53] in which the treatment machine rotates about the patient continually delivering dose. Such treatment plans can cut the delivery time to as much as a third.[54] Delivery with arcs can result in a more conformal treatment and in a decrease in chest wall dose with the trade-off of increased low dose to the contralateral lung.[55,56] However, treatment with arcs has also been associated with more radiographic pulmonary changes in comparison to treatment with fixed field beam arrangements.[57]

The optimal time interval over which peripheral NSCLC should be treated is unknown. Just as there have been a range of lung SBRT dose schedules, there are varieties of delivery timetables. Fractions have been delivered in consecutive days or with breaks of varying duration. The uninterrupted approach to delivery may minimize malignant cell repopulation and for patients may be more convenient. The "gapped" approach theoretically may allow for more sub-lethal damage repair of normal tissues and a decrease in toxicity. The only randomized study to address this question compared patients with peripheral tumors treated in four fractions over either 4 or 11 days.[58] Overall quality of life scores were not different at 1 and 4 months between the groups, although patients in the 4-day group experienced a clinically meaningful worsening in dyspnea (expressed as a rate of grade two or higher events). There was an imbalance between treatment groups, however, with the 11-day cohort having worse respiratory symptoms at baseline. Late toxicity and disease control were not addressed by this study, leaving the optimal treatment duration undefined.

SBRT with particle therapy is also being explored in an attempt to minimize toxicity. Treatment with protons or carbon ions may alter toxicity profiles since they lack an exit dose when compared with photons. Particle treatment planning in the lung is complicated, however, as the air and soft tissue interfaces that move with respiration create distal range uncertainties. Also, treatment is often done with two to three beams which can generate larger volumes of high dose than photons, particularly in the chest wall with peripheral lesions.[59] Despite this, comparisons of particle versus photon plans for patients with tumors within 2.5 cm of the chest wall show that particles can still reduce the chest wall doses at all levels measured.[60] Particles also allow for sparing more of the lung, heart, and esophagus, but the clinical relevance of these findings is uncertain and specifically for patients with peripheral tumors, these at-risk organs are often far from the target, with already limited exposures to dose with photon-based SBRT.[61]

CONCLUSION

Regardless of delivery method and treatment schedule, SBRT is an effective and well-tolerated noninvasive treatment for medically inoperable patients with peripheral NSCLC. Prospective and retrospective studies of lung SBRT suggest that it has superior outcomes with minimal toxicity when compared with conventionally fractionated treatments. This toxicity appears dose schedule and location dependent, resulting in the concepts of peripheral and central lesions. These terms currently inform outcome analysis in lung SBRT as well as trial stratification. Investigations into the effectiveness of SBRT in operable patients as well as the optimal dosing regimen are ongoing.

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